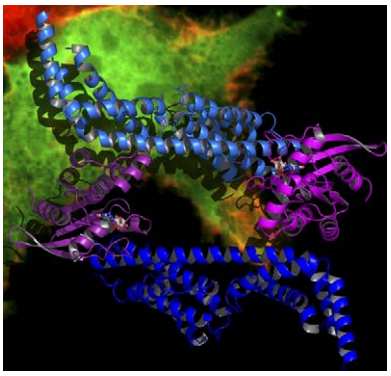
In This Issue

Cell



Yersinia YpkA, a Two-Headed Monster

PAGE 869

Bacteria of the genus *Yersinia* cause food poisoning and the plague. Prehna et al. now describe the crystal structure of YpkA, a *Yersina* virulence protein previously known to function as a serine/threonine kinase. This structure shows YpkA in complex with Rac, a Rho family GTPase that controls cell shape and movement. This structure reveals that in addition to being a kinase, YpkA also mimics a host guanine nucleotide dissociation inhibitor (GDI) in order to keep Rac in an inactive state. In directly targeting the Rho GTPases, YpkA hinders the immune response, because cells of the immune system must rapidly change their shape in order to engulf and destroy invading bacteria. Consequently, disrupting the interaction between YpkA and these GTPases makes the bacteria markedly less virulent in mouse models of infection.

All DNA Polymerases Are Not Created Equal

PAGE 881 and 893

Bacterial replicative DNA polymerases such as Polymerase III (Pol III) share no sequence similarity with other polymerases. Here, Lamers et al. and Bailey et al. present crystal structures of the catalytic subunits of Pol III from *E. coli* and *T. aquaticus,* respectively. The structures reveal that Pol III is strikingly different from other members of the canonical DNA polymerase families, including the eukaryotic replicative polymerases, but instead exhibit similarity to DNA polymerase β, a nucleotidyltransferase. These studies suggest that the DNA replication machinery in bacteria arose independently from those used in eukaryotes. At a more distant level, however, all DNA polymerases may share a common ancestor.

Histone Methylation with a Proline Twist

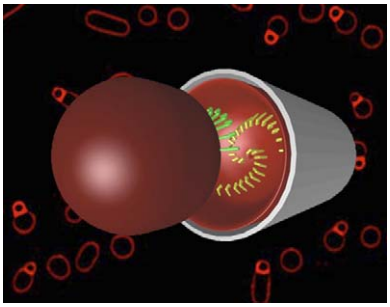
PAGE 905

The *cis-trans* isomerization of proline serves as a regulatory switch in signaling pathways. Nelson et al. find that the proline isomerase Fpr4 catalyzes the isomerization of histone H3 proline P30 and P38 in vitro and inhibits methylation of the neighboring H3 K36. Consistent with these findings, abrogation of Fpr4 catalytic activity in vivo increases H3K36 methylation and delays the induction of transcription of specific genes in yeast. These results identify proline isomerization as a novel noncovalent histone modification that regulates transcription and provides evidence for crosstalk between histone lysine methylation and proline isomerization.

Double Zipper for Spore Formation

PAGE 917

A key step in bacterial spore formation is engulfment, during which one bacterial cell (the mother cell) engulfs another (the forespore) in a phagocytosis-like process that normally requires the DMP proteins. Now, Broder and Pogliano describe a second mechanism of engulfment that involves two proteins, the forespore protein SpoIIQ and the mother-cell protein SpoIIIAH, which are essential for engulfment to occur when DMP activity is reduced. These two proteins mediate engulfment through a zipper-like interaction. These results suggest the existence of two separate engulfment machineries that compensate for one another, thereby rendering the process more robust.



Domains Not HAMPered by Turning

PAGE 929

HAMP domains are frequently found in prokaryotic transmembrane receptors. Because HAMP domains are continuous with the last membrane-spanning helix in a wide range of receptors, it is of particular interest for understanding signal propagation across membranes. Hulko et al. report the solution structure of an archaeal HAMP domain. This structure reveals a parallel, four-stranded coiled coil formed by dimerization of two helices from each monomer. The unusual interhelical packing that is observed suggests a model for transmembrane signal transduction in which the helices rotate by 26° like a cogwheel, along an axis perpendicular to the membrane.

SIRT4 Regulates Insulin Secretion

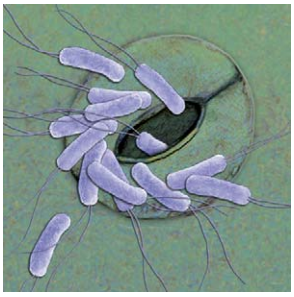
PAGE 941

Sir2 is an NAD-dependent deacetylase that connects metabolism with longevity in yeast, flies, and worms. Haigis et al. show that a mammalian Sir2 homolog, SIRT4, is a mitochondrial enzyme that ADP-ribosylates glutamate dehydrogenase (GDH) to inhibit its activity. The metabolism of glutamate and glutamine by GDH generates ATP, which promotes insulin secretion. In both SIRT4 knockout mice and in mice fed a calorie-restricted diet, pancreatic β cells show enhanced insulin secretion following amino acid stimulation. These results indicate that SIRT4 functions in the mitochondria of β cells to repress GDH activity, thereby downregulating insulin secretion in response to amino acids. Moreover, these effects are alleviated by calorie restriction.

Wnt Signaling Meets the Energy Bar

PAGE 955

The TSC2 tumor suppressor inhibits mTOR kinase, a key regulator of cell growth. Inoki et al. show that Wnt activates mTOR signaling via the kinase GSK3. GSK3 inhibits the mTOR pathway by phosphorylating TSC2 in a manner dependent on priming phosphorylation by the AMP-activated protein kinase, which is activated by low cellular energy. In this way, the sequential phosphorylation of TSC2 integrates both Wnt signaling and the energy status of the cell. In addition, inhibition of mTOR by rapamycin blocks Wnt-induced cell growth and tumor development, suggesting that rapamycin, an mTOR inhibitor, may have therapeutic potential for the treatment of cancers with activated Wnt signaling.



Closing the Door on Plant Pathogens

PAGE 969

Stomata are pores on the surface of leaves in vascular plants that regulate the transpiration of water and gas exchange. Because the plant surface is protected by a waxy layer that is difficult to penetrate, stomata have also been thought to be major points of entry for pathogens. Melotto et al. now provide evidence that stomata close in response to bacterial invasion and that successful pathogens suppress the closure of stomata to gain access to the nutrients in the leaf interior. The study demonstrates an active role for stomata in plant innate immunity.

Presenilin Springs a Ca2+ Leak

PAGE 981

Mutations in presenilins account for roughly 40% of familial cases of Alzheimer's disease. Athough these mutations are known to alter calcium (Ca^{2+}) signaling in cells, the underlying basis for this phenomenon has been unclear. The work of Tu et al. provides evidence that presenilins may function as a leak channel in the endoplasmic reticulum to control the Ca^{2+} content of intracellular stores. As a consequence, mutations in presenilins that are found in familiar cases of Alzheimer's disease alter the conductance of intracellular Ca^{2+}. These results suggest that blocking Ca^{2+} signaling may have therapeutic potential in the treatment of Alzheimer's disease.

Small Molecules Hold Steady

PAGE 995

General methods to perturb gene function at the level of DNA and mRNA are widely used, however there are no general methods to directly target proteins in mammalian cells. Banaszynski et al. have developed a strategy to conditionally regulate the stability, and thus function, of specific mammalian proteins. Specificity is achieved by fusing any gene of interest to an engineered "destabilizing domain," which causes the fusion protein to be susceptible to degradation. Stability is conferred by a cell-permeable small molecule that binds tightly to the destabilizing domain, allowing for rapid, reversible, and dose-dependent regulation of protein targets.